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Genetic abnormalities in childhood acute lymphoblastic leukemia at Hue Central Hospital, Vietnam

Nguyen Thi Kim Hoa
Ph.D Student, Faculty of Medicine and Pharmacy, Hue University, Hue, Vietnam

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Abstract

Aim: Acute lymphoblastic leukemia (ALL) is the most common malignant disease in children. Genetic abnormalities have been recognized to have prognostic or therapeutic relevance. In this study, we aimed to analyze the genetic abnormalities in childhood acute lymphoblastic leukemia patients which impact treatment and prognosis.

Material and Methods: It was a descriptive cross-sectional study on childhood acute lymphoblastic leukemia patients who admitted to the hospital between April 2018 and May 2022.

Results: There were 83 new patients, the male to female ratio was 1.37:1. The mean age was 5,18 ± 3,46 years. The most common symptoms were anemia (84.3%), fever (55.4%), hepatomegaly (53%), splenomegaly (45.8%), enlarged lymph nodes (45.8%), bleeding (34.9%) and bone pain (26.5%). Regarding laboratory features, 30.1% of the patients had white blood cell (WBC) ≥ 50x109/l, 74.5% of the patients had platelet (PLT) < 100x109/l, 90.3% of the patients had blood hemoglobin level (Hb) < 11 g/dl. Genetic analysis showed that 12.1% of patients have TEL/AML1, 4.8% of patients have BCR/ABL1, 3.6% of patients have E2A/PBX1, 2.4% of patients have MLL/AF4 and 1.2% of patients have SET/NUP214.

Discussion: The most common clinical presentations were anemia, fever, hepatosplenomegaly, bone pain and bleeding. Genetic abnormalities determine the prognosis and adjust the treatment for patients.

Keywords

Acute Lymphoblastic Leukemia, Children, Genetic Abnormalities

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Corresponding Author: Nguyen Thi Kim Hoa, Ph.D Student, Faculty of Medicine and Pharmacy,, Hue University, 6 Ngo Quyen Street, Hue, Vietnam.
E-mail: kimhoa.fmi@gmail.com P: +84 935 645836
Corresponding Author ORCID ID: https://orcid.org/0000-0003-2525-4368

Introduction

Acute leukemia is the most common cancer in children and teenagers, accounting for 25% of all childhood cancers [1]. It is a disease of the hematopoietic system characterized by the uncontrolled proliferation of one or more malignant immature cell lines. In acute leukemia, acute lymphoblastic leukemia (ALL) accounts for about 75%. The disease can easily lead to early death if not diagnosed and treated promptly. The incidence of acute lymphoblastic leukemia is about 2-5 cases per 100,000 children and ALL is the most common in children aged 2-5 years.

In developed countries, over the past 30 years, the effectiveness of treatment for acute lymphoblastic leukemia is gradually improving, the 5-year disease-free survival rate after commencing treatment is 80% [2]. In the US, this rate is up to 95% [1]. The detection of gene mutations helps to diagnose accurately and improve treatment [1, 3].

Many prognostic genetic markers of acute lymphoblastic leukemia have been identified, including genetic hybridization (BCR/ABL1, TEL/AML1, E2A/PBX1, MLL/AF4) and (hyper/hypoploidy), immune phenotypes (such as T/B cell markers).

Therefore, I carried out this study to describe clinical and laboratory characteristics of childhood acute lymphoblastic leukemia, and identify some of the genetic changes in acute lymphoblastic leukemia.

Material and Methods

Patients

Eighty-three patients were diagnosed with ALL at Hue Pediatric Center- Hue Central Hospital from April 2018 to May 2022. All ethical regulations were followed, and this study was approved by the Hue Central Hospital Ethics Committee (Institutional Review Board No. 18/NCKH-BVH). Consent was obtained from all participants in this study.

Method

This is a descriptive cross-sectional study. We described clinical presentations, laboratory tests and genetic tests. Genetic tests were done with Hemavisio28N kits which was a multiplex-RT-PCR test.

The diagnosis of ALL on admission was made on the basis of bone marrow morphology, which showed more than 20% of leukemic blasts. According to the results of flow cytometry, acute lymphoblastic leukemia was diagnosed.

Data were analyzed according to age, gender, clinical presentations, laboratory tests, and genetic tests. All statistical analysis was performed using SPSS v.18.0 (IBM Corp, Armonk, NY).

Results

A total of 83 new patients with ALL were identified from April 2018 to May 2022 who met eligible criteria. Among these patients, 48 were males and 35 were females, the male to female ratio was 1.37:1. The mean age was 5,18 ± 3,46 years. The peak incidence of ALL occurred in the age group (1-< 10 years), accounting for 79.5% (Table 1). There were 59,0% of patients with standard risk, and 41,0% of patients with high risk. The percentages of B-ALL and T-ALL were 85.5% and 14.5%, respectively.

Regarding clinical presentations, the mean time from the onset of symptoms to the hospital admission was 23.0 ± 23.7 days. The most common symptoms were anemia (84.3%), fever (55.4%), hepatomegaly (53%), splenomegaly (45.8%), enlarged lymph nodes (45.8%), bleeding (34.9%) and bone pain (26.6%). There were two cases with testicular involvement (2.8%).

For laboratory features, 30.1% of the patients had white blood cell (WBC) ≥ 50x109/l, 74.5% patients had platelet (PLT) < 100x109/l, 90.3% patients had blood hemoglobin level (Hb) < 11 g/dl. The mean values of blast cells in the bone marrow and peripheral blood were 14 ± 18 % and 156,5 ± 21,5 %, respectively.

Regarding biochemical tests, renal failure at the time of admission accounts for a very small percentage (1.2%), and 37.5% of patients have elevated transaminase. Most patients had increased LDH (89.9%) and uric acid (79.7%) levels. Nearly ¼ of patients had CRP > 8 (27.1%). There were no patients with CNS involvement at the time of diagnosis.

In 32 cases with chromosomal testing, the percentage of abnormal chromosomal preparation was low, only 9.4% of children with hyperdiploid chromosomes and 3.1% of children with extra chromosomes (Table 2).

In gene testing on 83 ALL patients, there were 10 patients with TEL/AML1 fusion (12.1%), 4 patients with BCR/ABL1 fusion (4.8%), 3 patients with E2A/PBX1 fusion (3.6%), 2 patients had MLL/AF4 fusion (2.4%) and 1 patient had SET/NUP214 fusion (1.2%) (Table 3).

Table 1. General characteristics of patients

Characteristics	Number of patients	Percentage of patients (%)
Gender		
Male	48	57.8
Female	35	42.2
Mean ages	5.18 ± 3.46	
Age group		
< 1 year old	5	6.0
1- < 10 years old	64	79.5
≥ 10 years old	12	14.5

Table 2. Chromosome results from bone marrow cells

Chromosome result	ALL	
	Number	Percentage (%)
Normal	28	87,5
Hyperdiploid	3	9,4
Hypodiploid	0	0
Addtitional mutation	1	3,1
Total	32	100

Table 3. Common fusion genes in ALL

Genetic expression	Number	Percentage (%)
TEL/AML1- t (12;21) (p13;q22)	10	12.1
BCR/ABL1- t (9;22) (q34;q11)	4	4.8
E2A/PBX1 – t (1;19) (q23;p13)	3	3.6
MLL/AF4- t (4;11) (q21;q23)	2	2.4
SET/NUP214- t (9;9) (p34;q34)	1	1.2
No expression	63	75.9
Total	83	100

Discussion

The male/female ratio was 1.37:1 and the mean age was 5.18 ± 3.46 years, similar to some studies by Fadoo, Al-Sudairy and Yasmeen [4-6]. The highest rate was in the age group (1-<10 years old), accounting for 79.5%, similar to the reports in Pakistan and Saudi-Arabia [4, 5, 7]

The mean time from symptom onset to hospital admission was 23.0 ± 23.7 days (range 1-90 days). The period was shorter than Robazzi's result [8], and longer than the result of some authors [4, 5]. The cause may be that the early symptoms of ALL resemble other common diseases, or the family's economic difficulties, so parents could not bring their children to the hospital in time.

The most common symptom in our study group was anemia, accounting for 84.3%, followed by fever (55.4%), hepatomegaly (53%), splenomegaly (45.8%), lymphoadenopathy (45.8%). Other manifestations included: bone pain (26.5%), hemorrhage (34.9%), testicular infiltration (2.8%). The cause of these manifestations was explained by the proliferation of immature cells in the bone marrow, which crowded out the normal development of hematopoietic cell lines, leading to anemia and at the same time neutropenia leading to fever and easy infection. Subsequently, the immature cells infiltrated the organs in the body, leading to lymphadenopathy and hepatosplenomegaly. Fadoo et al in their study also showed similar clinical manifestations with almost similar frequency [4]. In our study results, the average temperature at admission was 37.8 ± 0.9 degrees, ranging within 37-40 degrees Celsius.

Regarding cell lineages, B-call lineage accounted for a high percentage (85.5%), and T-cell lineage accounted for 14.5%. The result was similar to the results of studies in developing countries. According to Fadoo, there were 78.5% of B-cell patients and 17.5% of T-cell patients. According to Al-Sudairy, there were 89.5% of pre-B cell patients and 10.5% of T-cell patients [4, 5].

Regarding peripheral blood, there were 30.1% of patients with white blood cell count ≥ 50x109/l, similar to the result of Fadoo's study in Pakistan, with 28.8% [4], and higher than that of Pui (20%) [9], or 21.7% by Al-Sudairy [5]. Patients with elevated leukocytes are at risk for tumor lysis syndrome and have a poor prognosis [9]. Moreover, patients with elevated white blood cells often have elevated LDH levels [10]. It was notable in the white blood cell count that the neutrophil count was reduced, with a mean of 4.1 ± 11.3 x109/l. A low threshold of neutrophils is the cause of fever and infection in most patients, especially when chemotherapy begins. Regarding platelet count, there were 74.5% of patients with platelets < 100x109/l. Regarding hemoglobin level, there were 90.3% of patients with hemoglobin < 11g/dl.

When performing bone marrow aspiration, the result showed that the mean peripheral blood blast was 32.6 ± 29.1%, and the bone marrow showed the mean blast value of 61.6 ± 20.3%, fluctuating from 20 to 98%.

In terms of biochemical tests, the results of our study showed that one patient (1.2%) had a renal failure at the time of admission, and 32.5% of patients had elevated liver enzymes, consistent with the research results of some authors around the world [11]. The most common cause of kidney failure is tumor lysis syndrome, where cancer cells die on their own in large numbers, or under the influence of chemotherapy. 89.9% of patients showed increased LDH and 20.3% of patients had increased uric acid; 27.1% of patients had elevated CRP. According to Shimony, CRP is a sensitive biomarker to find febrile neutropenia and blood stream infections [12]. Considering the cerebrospinal fluid at the time of admission, 100% of patients had CNS1, much higher than the study of other authors. According to Al-Sudairy, 83% of patients had CNS1, 11.8% of patients had CNS2 and 5.2% of patients had CNS3 [5], or according to Fadoo, 93.4% of patients had CNS1, 5.8% had CNS 2 and 0.8% of patients had CNS3 [4].

The percentage of abnormal chromosomes was low, 9.4% of patients had hyper diploid chromosomes, and 3.1% of patients had extra chromosomes. Compared with other studies, according to Fadoo, up to 10.7% of patients had chromosomal hyperdiploidy, 5.1% of patients had hypodiploid and 84.2% of patients had a normal chromosome set [4]. According to Al-Sudairy, 24.6% of patients had hyperdiploid chromosomes. The reason for low results may be a small sample, not being able to reflect properly. In ALL, patients with hyperdiploid have a better prognosis [5].

The results of the analysis with multiplex PCR showed that 12.1% of patients had TEL/AML1, 4.8% of patients had BCR/ABL1 fusion, 3.6% of patients had E2A/PBX1 fusion, 2.4% of patients had MLL/AF4 fusion and 1.2% of patients had SET/NUP214 fusion. Our results had some similar figures, and some were much lower than those of other authors. According to Fadoo, the expression percentage of fusion genes BCR/ABL1, TEL/AML1, and MLL/AF4 were 7.3%, 13.2%, and 4.6%, respectively [4]. According to Al-Sudairy, the rate of BCR/ABL1 fusion was 4.2% and the rate of E2A/PBX1 and MLL/AF4 fusions were 3.6% and 2.5%, respectively [5]. With the multiplex-PCR, our result found new fusion comparing with other previous results in Vietnam. It was SET/NUP214 fusion. This fusion gene often occurs in T-ALL and is still poorly understood [13]. The cause of the difference in the ratio can be explained by the small sample, not being able to represent. According to Inaba, the fusion gene TEL/AML1 has an excellent prognosis, and fusion gene E2A/PBX1 has a favorable prognosis. In contrast, the fusion gene BCR/ABL1 has a poor prognosis and need to add tyrosine kinase inhibitors in treatment [14]. Similar, the fusion gene MLL/AF4 also has a dismal prognosis [14].

Conclusion

The most common symptoms in acute lymphoblastic leukemia are anemia, fever, hepatomegaly, splenomegaly, peripheral lymphadenopathy, hemorrhage, and bone pain.

Gene mutations detection plays a crucial role in the prognosis and modification of treatment for patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest
The author(s) declared no conflicts of interest.

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